REMARKS

Claims 1, 4, 7, 8 and 10-13 and 15-19 are pending.

While all claims are now listed as rejected in the last Office Action, Applicants point out that claims 7 and 8 were allowed in the Office Action of 08 November 2005), and Applicants thus presume that the Examiner has inadvertently listed these claims as rejected in the last Office Action, and request clarification.

Likewise, while all claims are now listed as rejected in the last Office Action, Applicants point out that claims 16-19 were indicated as being allowable in the Office Action of 08 November 2005, provided that they were amended to recite "hypermethylation...", which they were, and Applicants thus presume that the Examiner has inadvertently listed these claims as rejected in the last Office Action, and request clarification.

Applicants acknowledge the Examiner's maintained rejection of claims 1, 4, 7-8, 10-13 and 15-19, under 35 U.S.C. § 112 ¶1, based on alleged lack of *written description* for contiguous CpG island sequence that comprise SEQ ID NO:36 or 37. Applicants respectfully traverse this rejection.

Applicants acknowledge the Examiner's maintained rejection of claims 1, 4, 7-8, 10-13 and 15-19 under 35 U.S.C. § 112 ¶1, based on alleged lack of *enablement*. Applicants respectfully traverse this rejection.

A Declaration (unsigned) by Dr. Kurt Berlin is included to support the present Response and Amendment, and the *signed* Declaration will follow immediately upon receipt from Dr. Berlin who is in Germany.

No new matter has been added.

Rejections under 35 U.S.C. § 112, ¶1

Written description:

The Examiner has maintained the rejection of claims 1, 4, 7-8, 10-13 and 15-19, under 35 U.S.C. § 112 ¶1, based on alleged lack of written description for "contiguous CpG islands that comprise of SEQ ID NO:36 and 37.

Specifically the Examiner urges (citing The Regents of the University of Calif. v. Eli Lilly) that a generic statement defining a genus of nucleic acids by function is not enough to provide adequate written description (Office Action of 08 November 2005 at page 4).

Applicants respectively reassert and reaffirm the arguments of record, that in the present case applicants do not merely define a genus by functional activity, but rather the specification at page 5 and 8 teaches a formula; namely, "a CpG island sequence associated with a particular SEQ ID NO sequence of the present invention is that contiguous sequence of **genomic** DNA that encompasses at least one nucleotide of the particular SEQ ID NO sequence, and satisfies the criteria of having both a frequency of CpG dinucleotides corresponding to an Observed/Expected Ratio >0.6), and a GC Content >0.5." Physical properties and structure are also implicit within this definition, because the sequence is anchored at a precise genomic position, and the definition absolutely requires that the associated sequence is contiguous with the portion of the CpG island. Contrary to the Examiner's urging, the recited genera (CpG island sequences comprising SEQ ID NO:36 [or 37]) are not merely defined by functional language, but rather are explicitly defined by the core SEQ ID NO:36 sequence and the recited formula describing the larger CpG island, and the fact that the sequence is anchored at a precise genomic position. Therefore, the larger genomic CpG island is adequately defined and described by the core sequence and the formula.

Applicants point out that the Examiner's own example (see Office Action page 4):

**********(SEQ ID NO:36)*******(CpG)******

Illustrates that applicants' written description is adequate and commensurate in scope with the instant claims, because it has enabled the Examiner to present a species of applicants' claimed genus, based on the spectication teachings; the core SEQ ID NO:36 and applicants CpG island formula and the fact that this is a contiguous genomic sequence. Additionally, as taught by applicants, and as recognized by the Examiner in presenting this example, the CpG dinucleotide sequences are the precise defined sequences that are assayed, regardless of their position within the larger CpG island, in determining methylation state. A representative number of sequences is

provided by the fact that SEQ ID NO:36 is explicitly recited in the context of a contiguous 0.2 to about 1Kb according to the disclosed formula and definition of CpG island. For example, the following are species in the size range of 0.2 to 1.Kb are represented in the specification:

**********(SEQ ID NO:36)*******(CpG)******

**********(SEQ ID NO:36)*******(CpG)****

**********(SEQ ID NO:36)*******(CpG)**

**********(SEQ ID NO:36)*******(CpG)******

*******(SEQ ID NO:36)*******(CpG)****

(SEQ ID NO:36)****(CpG)**

*(SEQ ID NO:36)*******(CpG)*

Public policy considerations. Applicants are entitled to claims that are commensurate in scope not only with what applicants have specifically described and exemplified, and with that which one of skill in the art could obtain by virtue of that which the applicants have disclosed. In this instance, applicants have disclosed and taught portions of larger CpG islands, and importantly, have defined these larger CpG islands by applicants' formula. The sequence, formula and the fact that the island is a *contiguous* genomic DNA sequence adequately defines the CpG island. Applicants are the first to identify and recognize the recited utilities of these defined CpG islands. These claimed sequences are not like those of EST sequences for which no metes or bounds are available.

It is unfair and unduly limiting and contrary to the public policy upon which the patents laws are based to require applicants to limit the claims to the exact sequences exemplified, when the application clearly teaches how to make and use nucleic acid sequences that contain the core SEQ ID NOS:36 and 37 sequences. See, for example, *In re Goffe*, 542 F.2d 801, 166 USPQ 85 (CCPA 1970):

> for the Board to limit appellant to claims involving the specific materials disclosed in the examples so that a competitor seeking to avoid infringing the claims can merely follow the disclosure and make routine substitutions "is contrary to the purpose for which the patent system exists - to promote progress in the useful arts."

The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the disclosure. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions. *In re Sus and Schafer*, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304.

If applicants are required to limit the claims as suggested by the Examiner, then those of skill in the art can, by virtue of the teachings of this application, readily prepare markers from the respectively larger contiguous CpG islands, thereby practicing what is disclosed in the application, but avoiding infringing such limited claims. The instant application provides a broader disclosure; and having done so, places the public in possession of such knowledge. Having provided this disclosure, it permits others to benefit therefrom. Those of skill in the art should not be permitted to practice what is taught in the application, but avoid infringing the claims. To permit that is contrary to the intent of the United States patent law. Small early-stage companies can ill-afford to dedicate their innovations to the public.

Applicants, therefore, respectfully request withdrawal of the Examiner's rejection of claims 1, 4, 7-8, 10-13 and 15-19 under 35 U.S.C. § 112 ¶1, based on alleged lack of written description.

Additionally, applicants point out that claims 16-19 do not recite the larger CpG island, and therefore should not have been included in this rejection in the first place. Moreover, these claims were indicated as being allowable in the Office Action of 08 November 2005, provided that they were amended to recite "hypermethylation...", which they were. Applicants thus presume that the Examiner has inadvertently listed these claims as rejected in the last Office Action, and respectfully request allowance of these claims.

Further Rejections under 35 U.S.C. § 112, ¶1

Enablement:

The Examiner has maintained rejections of claims 1, 4, 7-8, 10-13 and 15-19 under 35 U.S.C. § 112 ¶1, based on alleged lack of enablement.

Specifically, the Examiner urges that the specification has not taught "a predictable correlation between [cancer and] nucleic acids which are coordinately methylated contiguous CpG island sequences that comprise SEQ ID NOS:36 and 37," and "therefore, it is unpredictable that coordinately methylated contiguous CpG island sequences that comprise SEQ ID NOS:36 and 37 are indicative of cancers absent unpredictable and undue experimentation." Additionally, citing Toyota et al., the Examiner urges that "the art does not support the idea that all contiguous CpG islands are associated with cancer...." The Examiner urges that Toyota teaches a detailed analysis

of CpG islands within the CACNA1G gene, stating that Toyota teaches "eight regions, each behaving differently" (regions 1 and 2 being concordant, regions 5, 6 and 7 behaving differently than regions 1-3, and regions 4, and 8 behaving differently again). The Examiner thereby concludes that "with respect to hypermethylation in cancer, the CpG region upstream of CACNA1G appears to behave independently" (citing page 4538, col. 1), and "therefore, since the art provides examples where CpG islands act in predictable ways (applicant) and examples where CpG islands act independently [Toyota, as construed by the Examiner], it is unpredictable whether the instant CpG islands act in a predictable or independent manner," and "therefore, it is unpredictable that coordinately hypermethylated contiguous regions comprising SEQ ID NOS:36 and 37 are associated with cancer" (Office Action of 08 November 2005 at page 8).

The Examiner has additionally cited Pao as teaching that among 11 individual CpG sites spanning the whole island, not all CpGs were hypermethylated even when adjacent to CpGs that were hypermethylated (*e.g*, that some adjacent CpGs were resistant or protected from hypermethylation), and additionally that the methylation patterns were dependent upon the tissue type. (Office Action at page 9), such that a single nucleotide would not allow predictable association absent further experimentation to determine the pattern in a particular tissue type.

The Examiner has additionally cited Cameron as teaching that the p15 CpG island methylation is heterogeneous, and thus does not support that a single dinucleotide may be representative of an entire CpG island.

Applicants respectfully traverse this rejection, because the Examiner has **substantially** misconstrued the teachings of Toyota, Pao and Cameron, which actually support applicants' position.

First, applicants reaffirm and reassert the Declaration of Dr. Cathy Lofton Day, already of record, and which will therefore not be reiterated herein.

Second, we are in agreement with the Examiner that Toyota teaches "examples where CpG islands act independently." However, that is not the relevant question here. The relevant question is whether the CpG dinucleotide sequences within a given CpG island behave coordinately. Here,

the teachings of Toyota are in agreement with the applicants currently recited claims.

Specifically, Toyota initially describes/defines a large 4Kb region, based on a definition of having a GC content of 0.67; CpG/GpC ration of 0.78; and a total of 305 CpG sites in a 4-kb region (Toyota at pate 4536 column 2 middle of 1st full para), and divides this 4kb region into 8 subregions. However, Toyota notes that this region is considerably larger that typical CpG islands (Toyota at page 4537, column 2, 1st full para), and he explicitly concludes that "with regards to hypermethylation in cancer, the CpG-rich region upstream of CACNA1G appears to be composed of two CpG islands that behave independently" (MINT31 regions 1 and 2 corresponding to the upstream CpG island 1; the 5' regions 5-7 of CACNA1G in the downstream CpG island 2; and regions 3, 4 and 5 between CpG island 1 and 2, behaving differently. Toyota concludes (page 4540, at end of carryover para) that "methylation of MINT 31 appears to be independent of methylation of CACNA1G, suggesting that they are two distinct CpG island regulated by different mechanisms." Significantly, therefore, Toyota teaches that while different CpG islands within a gene area can behave differently or independently, the subregions within a given CpG island, for example regions 1 and 2 of island 1 and regions 5-7 of island 2, behave coordinately and define the behavior of the CpG island which comprises the subregions.

Therefore, Toyota like the vast bulk of art in this area, is fully consistent with the teachings of the present invention which teach that the CpG dinucleotides within a given contiguous CpG island are coordinately methylated.

Third, the teachings of Pao that not all CpGs in a CpG island were hypermethylated even when adjacent to CpGs that were hypermethylated (*e.g*, that some adjacent CpGs were resistant or protected from hypermethylation), does not run counter to applicants recitation of coordinately methylated CpGs, because applicants recitation does not require that *all* CpGs within a CpG island are coordinately methylated, but rather only that the methylation change (*e.g*, hypermethylation) of the those CpGs that are differentially methylated between normal and cancer, is a methylation change that is coordinate, so that all differentially methylated CpG are either up-methylated (hypermethylated to some extent), or all down-methylation (hypomethylated to some extent).

Applicants claims reflect the fact that within a particular CpG island, the change in methylation of those CpGs that do undergo a methylation change, is coordinate (i.e., coordinately hypermethylated or coordinately hypomethylated). It is irrelevant that some CpGs are protected from, or resist hypermethylation for example. The claims are drawn to coordinately methylated CpGs with the CpG island, and do not necessarily require that *all* CpGs are differentially methylated between normal and cancer. In fact the CpGs of Pao follow this pattern in that while not all CpGs participate in differential methylation between normal and abnormal tissue, those that do participate do so in a generally coordinate way, although the extent of hypermethylation is not identical between differentially methylated CpGs there is nonetheless coordinate methylation.

Fourth, the Examiners urging that teachings of Cameron that the p15 CpG island methylation is heterogeneous, and thus not support that a single dinucleotide may be representative of an entire CpG island is fundamentally flawed, because the methylation heterogeneity characterized in Cameron relates to heterogeneity in the specific CpGs sites hypermethylated between alleles. That is, like Pao, not all CpGs on both alleles undergo hypermethylation. However, those CpGs that do show hypermethylation are coordinately hypermethylated.

Therefore, applicants respectfully contend that the Examiner's position is entirely unsupportable in view of Toyata, Pao and Cameron, and that these references actually support applicants' position or coordinate hypermethylation within a CpG island.

Moreover, given the instant teachings and the state of the art, and fully consistent with Toyota cited by the Examiner, applicants contend that it would not entail undue experimentation to determine whether a CpG dinucleotide of the contiguous CpG islands that respectively comprise SEQ ID NO:36 or 37 is coordinately methylated with a CpG of SEQ ID NO:36 or 37. This is precisely what would be expected as described above, and in view of Toyota, Pao and Cameron cited by the Examiner. Such a CpG island is readily identifiable and analyzable because it is structurally defined as being contiguous to applicant's disclosed SEQ ID NOS:36 or 37, and is further defined and describe by applicant's formula describe herein above. The level of skill in the

art is high, and given the instant teachings and those of the art, isolation of such a CpG island sequence from a cancer tissue and determining the methylation state of one or more CpG residues therein relative to a control, could be done by one of ordinary skill in the art in a matter of a few days or a week using standard DNA manipulation methods and methylation assays available at the time of filing of the present application.

Finally, a Declaration by Dr. Kurt Berlin is attached hereto in support of the present Response and Amendment. The declaration describes a paper (Eckhardt et al., *Nat Genet.* 2006 Dec;38(12):1378-85. Epub 2006 Oct 29) further confirming, as was appreciated in the art at the time of filing and as taught in the instant specification, that there is a significant correlation for co-methylation within CpG dense regions (*e.g.*, CpG islands) over the distance of up to at least 1,000 nucleotides in each direction from a particular determined CpG (see, *e.g.*, page 2, column 2, 1st full paragraph, of attached publication document). The Declaration additionally comments on and rebuts the Examiner's contentions, based on Toyota et al.

In light of the scope of the claims, the teachings in the specification, the presence of specific working examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in this art, and the predictability of the subject matter, it would not require undue experimentation for a person of skill in the art to practice the invention as claimed. Therefore, the specification is enabling for making and using the full scope of the claimed subject matter.

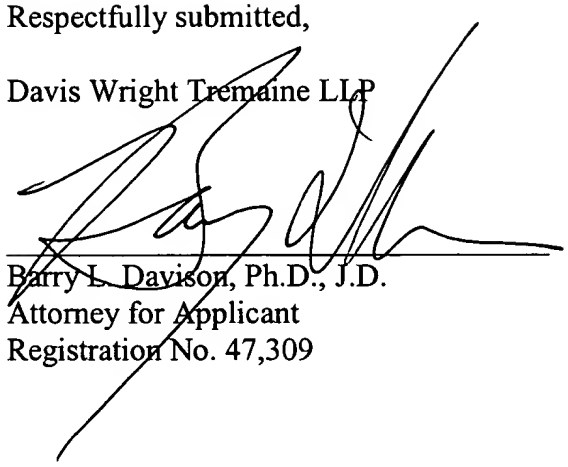
Applicants respectfully request that the rejection be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully request entry of the present Response and Amendment, and allowance of all pending claims. The Examiner is encouraged to phone Applicants' attorney, Barry L. Davison, to resolve any outstanding issues and expedite allowance of this application.

Respectfully submitted,

Davis Wright Tremaine LLP



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